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Nutritional neurobiology and central nervous system sensitisation: missing link in a comprehensive treatment for chronic pain?

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Increasing attention is being paid to dietary and nutritional factors in relation to chronic pain, not only for abdominal (i.e. visceral) pain, but also for other chronic (somatic) pain disorders, such as migraine headache, neuropathic, osteoarthritis, (post)cancer, and low back pain. A recent meta-analysis confirmed that nutritional interventions, especially an altered dietary pattern and an altered specific nutrient intake, can result in significant pain relief in patients having chronic pain.[1] Even though they may be merely secondary to the mechanical impact of weight loss, such clinical benefits may arise from a potential dietary link to CNS sensitisation.[2] CNS sensitisation, defined as 'an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity',[3] is a well-established feature in many chronic pain patients, including those with chronic spinal pain, post-cancer pain, fibromyalgia, osteoarthritis, and paediatric pain.

How can diet potentially contribute to CNS sensitisation? Poor diet (i.e. low fibre, energy-dense diet, etc.) is associated with oxidative stress, cell necrosis, and tissue damage throughout the body, each of which is a potential endogenous activator of Toll-like receptors (TLRs).[4] Upon activation, pattern-recognition TLRs trigger pro-inflammatory central immune signalling events,[4] including glial cell activation, which in turn results in low-grade neuroinflammation[5] (Fig. 1). Aberrant glial activity also causes astrocyte activation in the CNS, which leads to the production of pro-inflammatory substances by hypertrophied and activated astrocytes (astrogliosis).[6] Increased brain glial activation has been shown in patients with chronic pain, including those with chronic non-specific low back pain[7] and fibromyalgia.[8] Spinal-cord glial activation was found in patients having chronic lumbar radiculopathy pain.[9] In addition to TLRs (TLR-4 and TLR-2), another important trigger of microglial activation is the fractalkine receptor (CX3R1), which is a rapid and selective trigger of spinal dorsal horn microglia.[10] Animal models have shown that fractalkine plays an important role in the early activation of high-fat diet-induced hypothalamic inflammation.[11]

Aberrant glial activity has the potential to initiate CNS sensitisation through several mechanisms. Activated microglia have been identified as a major source for the synthesis and release of several neurotrophic factors, including brain-derived neurotrophic factor, which is responsible for increasing neuronal excitability by causing disinhibition in dorsal horn neurones in the spinal cord.[12] Aberrant glial activity is also accompanied by increased tumour necrosis factor-α, which in turn induces long-term potentiation,[13] leading to enhanced synaptic efficacy[14] and, ultimately, pain sensitisation.[13] Long-term potentiation and enhanced synaptic efficacy are (partly overlapping) key mechanisms underlying CNS sensitisation[15] and the formation of (maladaptive) pain memories in patients with chronic pain.

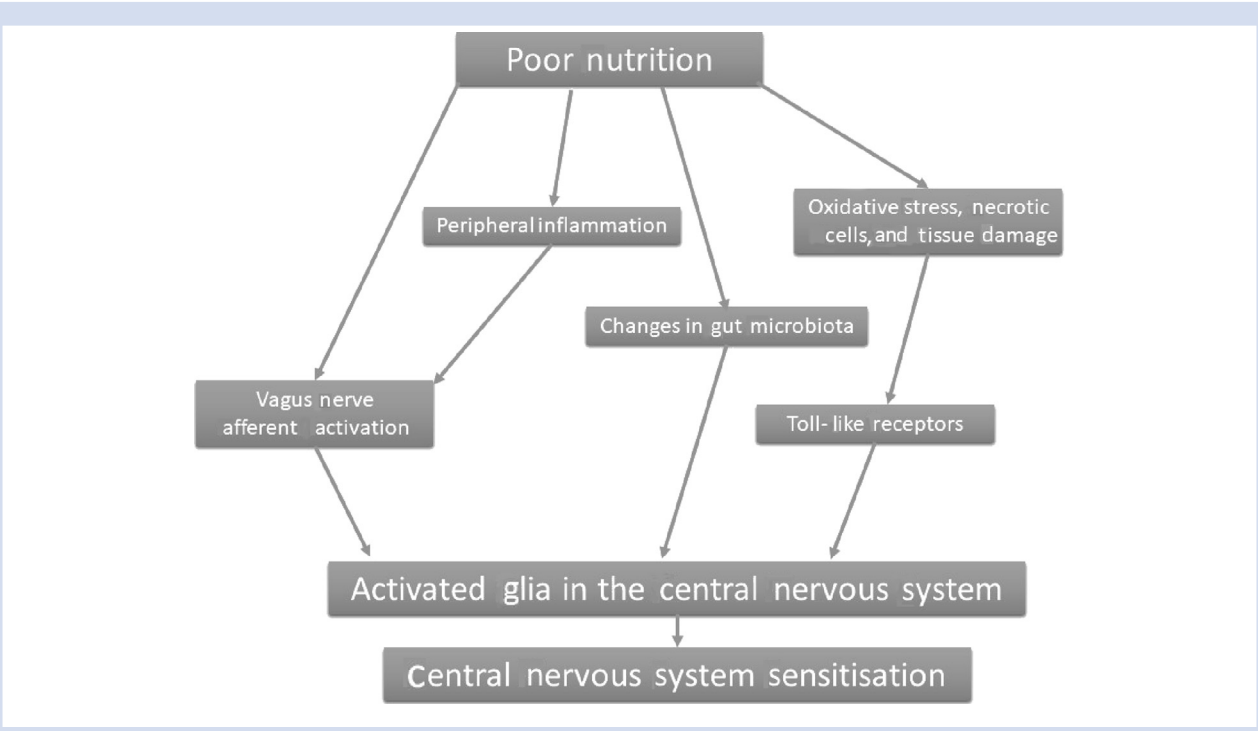

Fig 1. Mechanisms linking diet, neuroinflammation, and CNS sensitisation in chronic pain. The displayed interactions are based mainly on preclinical studies.

The peripheral pro-inflammatory effects of poor nutrition are well established,[16] generating another route through which diet can impact the CNS. Indeed, peripheral pro-inflammatory cytokines can cross the blood–brain barrier and migrate into the CNS. Conversely, human studies suggest that a diet rich in vegetables, fruits, healthy oils, and fibres exerts anti-inflammatory action.[17] In addition, other routes potentially explain how poor diet can trigger CNS sensitisation. High-(saturated) fat or energy-dense diet, and the pro-inflammatory mediators that come along, is sensed via vagal afferent nerves in the gastrointestinal system.[18] More specifically, enteroendocrine cells are the primary 'gut (chemo) sensors' dispersed throughout the gastrointestinal mucosa that secrete hormones and amines in response to the presence of three macronutrient types: carbohydrates, proteins, and lipids.[19] Vagal afferent neurones express receptors for regulatory peptides and molecules released from the intestinal wall, pancreas, and adipocytes, such as cholecystokinin.[20] This way, vagal afferent neurones inform the brain about dietary intake, which may in turn lead to microglial activation[18] (Fig. 1). An alternative route implies that increased peripheral (local gastrointestinal or systemic) inflammation activates vagal afferents (they have cytokine receptors), which in turn induces neuroinflammation.[21]

Moreover, diet-induced changes in gut-microbiota composition can also trigger vagal afferent activation[18] and (low-grade) gut inflammation.[22] Likewise, under free-fatty-acid-rich obese conditions, astrocytes participate in obesity-induced hypothalamic inflammation by promoting microglial migration and activation.[23] In animals, a caloric restriction diet (i.e. 6 weeks at 60% of the *ad libitum* food intake of their counterparts) inhibited neuroinflammation, including glial cell activation, and consequently decreased CNS sensitisation and pain behaviour.[24] The same researchers reported that such a caloric restriction diet in non-obese rats results in anti-nociceptive effects on postoperative pain, possibly mediated by inhibition of inflammation.[25] Taken together, it is plausible that an unhealthy diet characterised mainly by high-calorie intake (e.g. high saturated fat or energy-dense diet) is in part responsible for glial activation as observed in patients with chronic pain.

This idea of diet-induced (or diet-maintained) neuroinflammation is strengthened by a series of observations in humans. First, a cross-sectional study showed that markers of neuroinflammation are associated with peripheral glucose concentrations in patients having complex regional pain syndrome,[26] a severely debilitating subtype of chronic pain. Another cross-sectional study revealed that age-adjusted elevated concentrations of blood glucose and low high-density lipoprotein (HDL) cholesterol are each independently associated with higher chronic pain intensity.[27] Low HDL cholesterol concentrations might be the result of a low-grade inflammatory process in (some) patients with chronic pain.[27] Unsaturated fatty acids increase HDL (and in turn decrease blood cholesterol).[28] Therefore, it can be hypothesised that unsaturated fatty acids have the potential to reduce chronic pain intensity through the increase in HDL, although further research is needed to verify this.

Animal work revealed that high-glucose conditions facilitate CNS sensitisation through increasing expression and activation of high mobility group protein B1, a modulator of the inflammatory response, in dorsal root ganglion neurones.[29] Metformin, a drug for controlling blood sugar concentrations in diabetes mellitus, not only decreases body weight

in animals, but also decreases inflammation and CNS sensitisation (i.e. decreased sensitivity to mechanical and thermal allodynia).[30] The glucocorticoid system may be a potential mediator for the link between inflammation, glucose, and pain, as mice exposed to interleukin-1β showed increased blood glucose concentrations and pain behaviour via the activation of the glucocorticoid system.[31] This has obvious relevance to diabetics who may suffer from neuropathic pain, but may also be relevant to chronic pain independent of diabetes mellitus. Indeed, chronic widespread pain in humans, independent of diabetes, is associated with higher cortisol and fasting glucose.[32]

The link between glucose, inflammation, and pain is also supported by studies exploring the potential effect of a ketogenic diet in patients having chronic pain. A ketogenic diet is very high in fat, with sufficient protein and restricted carbohydrate intake. It alters cellular (including central neurone) metabolism so that ketones, produced by the liver, are burned instead of glucose: the restricted carbohydrate content of a ketogenic diet minimises glucose metabolism and increases ketolysis (i.e. the use of ketone bodies [acetone, acetoacetate, and β-hydroxybutyrate] as alternate energy sources).[33] Animal work showed that, after 3–4 weeks, such a ketogenic diet resulted in acute peripheral anti-inflammatory and hypoalgesic effects.[33] A similar effect is likely in humans,[34] but (randomised) interventional studies to confirm this hypothesis are lacking.[1]

When glycolytic enzymes are inhibited, pain thresholds increase (and consequently pain reduced).[35] This analgesic effect is mediated centrally,[36] and might involve increased brain/spinal-cord inhibition by adenosine.[37] Inversely, a high blood glucose concentration results in pain hypersensitivity probably by disrupting the functions of cell mitochondria and subsequent generation of reactive oxygen species and oxidative stress,[38] and the activation of microglia.[39] Therefore, the reduced CNS excitability[40] in response to a ketogenic diet may be—at least in part—attributed to its anti-inflammatory and antioxidant properties.[41] The reduced CNS excitability can also be triggered directly by ketones or low glucose, fatty acids, or downstream metabolic effects,[42] but animal work suggests that hypoalgesia does not result from direct actions of elevated ketones or decreased glucose.[43] Alternative explanations include activation of K1 channels, adenosine A1 receptors, or gamma-aminobutyric acid receptors, all causing hypoalgesia.[44] Still, the clinical utility of a ketogenic diet in patients having chronic pain remains to be established via randomised controlled clinical trials that should try to address the problems inherent to this type of nutritional intervention trials (including the difficulties of identifying a good control condition, with blinding, etc.).

Another hypothetical route through which diet can sustain or aggravate CNS sensitisation in chronic pain is the capacity of gut microbiota to regulate CNS neurotransmission. This includes the proposed ability of some microbial species to elevate concentrations of tryptophan and subsequently central signalling by serotonin,[45] a neurotransmitter important for brain-orchestrated endogenous analgesia.[46] A preclinical study revealed that secretory products from commensal bacteria derived from a healthy human donor contain serine proteases that suppress the excitability of dorsal root ganglion neurones via activation of protease-activated receptor-4.[47] Another animal study showed that commensal intestinal microbiota are necessary for normal excitability of gut sensory neurones.[48] These findings suggest that therapies that address microbial dysbiosis may also affect the excitability of primary afferent (nociceptive) neurones,[47] possibly reducing CNS sensitisation via a bottom-up route. It has been suggested that probiotics might restore balance of the gut microbiome and introduce beneficial functions to gut microbial communities, resulting in reduced gut inflammation.[49] Data provided by animal studies on visceral pain show that probiotics might exert a direct action through bacterial metabolites on sensitive nerve endings in the gut mucosa, or indirect pathways targeting the intestinal epithelial barrier, mucosal or systemic immune activation, and subsequent central neuronal system sensitisation.[50] However, even though many claims about causal relationships between gut microbiota and human behaviour are being made, methodologically sound research is often lacking.[51] Before claims about consideration of probiotics as a potential new therapeutic target in patients having chronic pain and CNS sensitisation can be made, findings from animal studies require examination in humans having chronic pain.

This model of diet-induced neuroinflammation and consequent CNS sensitisation (Fig. 1) provides a rationale for developing innovative treatments for patients with chronic pain, such as dietary interventions and pharmacological treatments. The model first requires further elaboration at the dietary level (i.e. which specific nutritional components play a role in the proposed diet–neuroinflammation–CNS sensitisation pathway?) and experimental testing in humans before causal inferences can be drawn.

Authors' contributions

Study design: JN
Review, analysis, and interpretation of literature data; data acquisition: all authors
Writing first draft: JN
Revising paper and approving final version: all authors

Declaration of interest

The authors declare that they have no conflicts of interest.

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'Plus ça change' for the future of sepsis?

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Question: How do you eat an elephant?
Answer: One bite at a time.

The articles in the recent special collection of the *British Journal of Anaesthesia* (https://bjanaesthesia.org/world-sepsis-day-2019) to mark World Sepsis Day (September 13, 2019) illustrate some of the complexities in understanding and addressing sepsis, one of the most challenging diseases to treat and a major killer. Although many of these articles increase our knowledge of the biology of sepsis, sepsis is not a single condition and the potential impact of infection on an individual can be unpredictable and significant. Changes in the epidemiology of sepsis as a result of modified diagnostic criteria add another dimension: the more we increase our overall knowledge, the more it requires re-examination and reconsideration of what we understand as sepsis.[1] One useful approach then is to acknowledge this complexity and utilise a multifaceted approach to improving recognition, diagnosis, and treatment as discussed by Nunnally.[2]

Early recognition of patients with, or at risk of developing, sepsis is key to timely and effective management. Campaigns to increase public awareness of sepsis have gone hand in hand with publications such as National Institute for Health and Care Excellence (NICE) guidance NG51, which have identified recommendations for managing suspected sepsis in the community and acute hospital settings.[3] Adoption of the UK National Early Warning Score (NEWS 2) facilitates earlier recognition of the deteriorating patient in hospital.[4] Running alongside a drive to recognise deterioration has been the implementation of response services such as Critical Care Outreach teams and prompt ward level management strategies that may have an impact on the morbidity and mortality associated with sepsis in hospital.[5] There is also a need to cohort people who need more than simple ward level care but do not require admission to critical care units. The ability to monitor the 'at risk' patient with an increased frequency of observations and more complex interventions should be delivered in an enhanced care area in a hospital. Development of these enhanced care services is one of the recommendations of the Faculty of Intensive Care Medicine's 'Critical Futures' Initiative in the UK and is a current Faculty work stream to develop guidance for UK hospitals.[6]

Not all deteriorating patients have sepsis, and not all patients with sepsis are the same. Determining the true incidence of sepsis and septic shock has definitional difficulties, but may also in part be attributable to better recognition in an ageing hospital population with increasing co-morbidities.[7] Sepsis is a syndrome in which the clinical presentation depends on the type of infection, patient comorbidities, patient immune response, and degree of organ dysfunction. This spectrum of physiological response and unpredictable outcome can, in extreme cases, lead to ICU admission, multiple morbidities, or even death. Approximately 30% of admissions to intensive care in England are attributable to sepsis with the most common site of infection being in the respiratory system.[8] ICU mortality caused by sepsis in some parts of the world has decreased, most likely because of early recognition and timely intervention. In a 12 yr review of survival from sepsis in the Australian and New Zealand intensive care database, mortality decreased from 35% to 18%, suggesting